REMARKS

Claims 1-3 and 5-34 are pending in the present application. Claims 10-31 are withdrawn as being drawn to a non-elected invention. For the reasons stated in the Applicants' response of August 17, 2005, the Examiner is requested to rejoin the withdrawn claims. Claims 1-9 and 34 are under examination. Claims 1, 6, 7 and 32 are amended. Support for claim 1 is found in original claims 4 and 15. Claims 6-7 are amended to change dependency from canceled claim 4 to claim 1. Claim 6 is also amended to add a period to the end of the claim. Claim 32 is amended to correct the allegedly unclear antecedent basis. Claims 33 and 34 are new. Support for new claims 33 and 34 is found on page 11, lines 5-7. Claim 4 is canceled. No new matter is entered by way of this amendment.

Rejections under 35 USC 112, second paragraph

Claim 32 is rejected under 35 USC 112, second paragraph as being indefinite. Applicants respectfully traverse.

Specifically, the Examiner states that there is insufficient basis for the phrase "said foaming." Claim 32 is amended to remove the allegedly unclear language. Accordingly, Applicants respectfully request the rejection be reconsidered and withdrawn.

Rejections under 35 USC 102

Claims 1-3 and 32 are rejected under 35 USC 102(b) as being anticipated by Nakari-Setala *et al. Cur. J. Biochem.* 248:415-423 (1997) ("Nakari-Setala"). Applicants respectfully traverse.

Claim 1 is drawn to method for decreasing the foam formation during cultivation of a fungal production host, characterized in that the process comprises the steps of genetically modifying the fungal production host in such a way that the fungal production host does not produce an essential amount of at least one of the proteins, polypeptides or peptides associated with foam formation during cultivation, the proteins, polypeptides or peptides being amphipathic

or hydrophobic proteins, polypeptides or peptides, not including lipopeptides or lipoproteins; and cultivating the fungal production host under suitable culture conditions.

In contrast, Nakari-Setala *et al.* disclose the isolation of the *hfb2* gene by heterologous hybridization and the isolation of HFBII, a hydrophobin protein, from *T. reesei* fungal spores by extraction with trifluoracetic acid/acetonitrile solution, and by bubbling from a lactose-based culture medium. Additionally, Nakari-Setala *et al.* teach that HFBII is found in submerged cultures when the fungus is grown, *inter alia*, on cellulose or lactose-containing media or other carbon sources, which usually promote extracellular hydrolase production. Moreover, Nakari-Setal *et al.* describe that *hfb2* expression is induced by N and C starvation, and by light; while a second hydrophobin, *hfbI,* is not expressed on media containing complex plant polysaccharides, including cellulose, xylan, cellobiose or lactose. Thus, Nakari-Setala *et al.* do not disclose all of the elements of the present invention.

The Examiner states that the Nakari-Setala *et al.* reference discloses a method for modifying and cultivating microorganisms belonging to *Trichoderma reesei* under various culture conditions in such a way that the microorganism does not produce an essential amount of hydrophobins. Thus, according to the Examiner, the microorganism does not significantly produce hydrophobins when cultured in the presence of glucose and/or in the dark.

Nevertheless, the Nakari-Setala *et al.* reference does not anticipate the instant claims. Nakari-Setala *et al.* only disclose the modification of the *culture conditions* of a microorganism, not the modification of the fungal production host itself, as is instantly claimed. Particularly, Nakari-Setala *et al.* observed, at the laboratory scale level, the effect of various carbon sources on the expression and production of hydrophobins. For example, Nakari-Setala *et al.* observed that *hfb I* is highly expressed in the presence of glucose and *hfb2* is expressed in the presence of a more complex carbon source, *e.g.* cellulose. Additionally, Nakari-Setala *et al.* observed that *hfb2* is also strongly induced by N and C starvation, by light and in conidiating cultures.

However, the culture conditions of Nakari-Setala *et al.* do not modify the microorganism itself. Moreover, the culture conditions do not modify the microorganism *genetically*.

The Examiner also asserts that Nakari-Setala *et al.* disclose that hydrophobins are associated with foam because Nakari-Setala *et al.* clearly describe that when hydrophobins are produced they are collected from foam formed in a cultivation medium upon bubbling.

However, it should be noted that the bubbling is made by bubbling air into the culture medium through a glass Pasteur pipette and the foam formed on the pipette surface was collected into a trifluoracetic acid/acetonitrile solution. The bubbling of air in a laboratory pipette has nothing to do with foam formation during the cultivation of a microorganism in a fermentor in the presence of aeration and agitation. Bubbles are formed in nearly any liquid if air is conducted through it.

Moreover, the reference of Nakari-Setala *et al.* does not teach how to decrease foam formation. The Nakari-Setala *et al.* reference is limited to the biological role of hydrophobins under various culture conditions.

Thus, the Nakari-Setala *et al.* reference does not anticipate claim 1. In order to anticipate a claim, each and every element of the claim must be disclosed in the reference. Because Nakari-Setala *et al.* fail to disclose the element of decreasing foam formation during cultivation of a fungal production host by "genetically modifying the fungal production host", Nakari-Setala *et al.* do not anticipate claim 1. Likewise, dependent claims 2-3 and 32-34 are also allowable, at least by virtue of dependency.

Rejections under 35 USC 103

Claims 1-9 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakari-Setala *et al.* (1997) in view of Wosten *et al. The Plant Cell*, 5: 1567-1574 (1993),

("Wosten *et al.*") and Spanu *et al. Physiological and Molecular Plant Pathology* 52: 323-334. Applicants respectfully traverse.

In order to establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Applicants submit that there is no suggestion or motivation to combine Nakari-Setala *et al.* with Wosten *et al.* and Spanu *et al.*

The Examiner asserts that, although the Nakari-Setala *et al.* reference does not teach the genetic modification of microbial genes associated with the regulation and production of hydrophobins, the Nakari-Setala *et al.* reference suggests this modification. Applicants respectfully disagree.

The Nakari-Setala *et al.* reference teaches that HFBII is located in spore walls and that the disruption of genes encoding such spore hydrophobins results in reduced spore hydrophobicity due to the loss of the outer rodlet layer of the spores. However, loss of *spore* hydrophobicity does not suggest that genetic modification of a fungal production host will lead to a decrease in foaming during cultivation. The vegetative cells, not the spore cells, of a production host are grown in a fermentor during cultivation because the object of cultivating a production host is protein or biomass production, not spore production. Thus, the Nakari-Setala *et al.* reference does not suggest the desirability of the claimed invention since Nakari-Setala *et al.* only teach the effect of spore hydrophobin gene disruption on spore hydrophobicity.

Likewise, the Spanu *et al.* reference does not suggest the desirability of the claimed invention. Although Spanu *et al.* teaches that the deletion of a specific hydrophobin in a microorganism results in a decrease in hydrophobicity, Spanu *et al.* do not teach how this decrease in hydrophobicity effects foaming in a culture solution. In fact, the microorganism of Spanu *et al.* is not cultivated in a culture solution. Thus, there is no motivation from the Spanu *et*

al. reference to combine the genetic modification disclosed therein with the microbial hydrophobin production of Nakari-Setala *et al.*

Furthermore, the Wosten *et al.* reference fails to suggest the desirability of the claimed invention. Wosten *et al.* disclose that the Sc3p hydrophobin from *Schizophyllum commune* forms aggregates when bubbling air through the culture medium or when grown in shaken cultures. The aggregation phenomenon disclosed in the Wosten *et al.* reference is so strong that the formed aggregates are clearly visible solids that can be centrifuged out from the culture solution. No observations regarding foaming are disclosed in Wosten *et al.* Thus, the Wosten *et al.* reference does not suggest that modifying the hydrophobin production of Nakari-Setala *et al.* will result in a decrease in foaming.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Applicants submit that nothing in the cited references suggests that the problem of foam formation could be solved by genetically modifying a fungal production host to not produce a hydrophobin. Moreover, it was unclear until the present invention whether or not the vegetative cells of a fungal production host could be cultivated in the presence of aeration and agitation due to the fragility of the cells.

Thus, for the reasons set forth above, the Examiner has not established a *prima facie* case. Accordingly, claim 1 is not obvious over combination of Nakari-Setala *et al.*, Spanu *et al.* and Wosten *et al.* Because claims 2-9 and 32-34 depend on claim 1 and incorporate all of its elements, claims 2-9 and 32-34 are allowable at least by virtue of their dependency. Accordingly, Applicants respectfully request the rejection be reconsidered and withdrawn.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Gerald M. Murphy, Jr. Reg. No. 28,977 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

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Respectfully submitted,

By _____

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